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Angiotensin II does not increase renal prostaglandin E_2 in response to pressure reduction

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Angiotensin II does not increase renal prostaglandin E_2 in response to pressure reduction. Whether angiotensin II (Ang II) stimulates renal secretion of prostaglandin E_2 (PGE_2) synthesized in response to pressure reduction was examined. PGE_2 and Ang II in aortic and renal venous plasma were measured before and during renal arterial constriction in anesthetized dogs, with or without an intrarenal arterial infusion of an Ang II antagonist, losartan potassium (1 mg/min), or saralasin (3 μg/min). In other anesthetized dogs, two doses of Ang II (30 and then 300 ng/min) were infused into the renal artery, and plasma Ang II levels and renal PGE_2 secretion were measured. When renal perfusion pressure was reduced to 75 and 45 mm Hg by constriction, the renal secretion of PGE_2 increased seven- and fourfold, respectively. Ang II levels in the renal venous plasma increased from 6.6 ± 1.8 to 21.7 ± 7.4 and then 48.1 ± 15.3 pg/ml (both $P < 0.05$) as the pressure decreased. Neither losartan nor saralasin suppressed the response of renal PGE_2 secretion to the pressure reduction. The intrarenal infusion of Ang II (30 ng/min) elevated the Ang II level in the renal venous plasma from 9.8 ± 4.6 to 33.7 ± 4.2 pg/ml ($P < 0.01$), but did not increase PGE_2 secretion. The higher dose (300 ng/min) of Ang II increased it, but the Ang II level in the renal venous plasma was 166 ± 63 pg/ml. These results suggest that the greater part of the increased renal synthesis of PGE_2 in response to pressure reduction is not mediated by Ang II.

When the renal artery is stenotic unilaterally and the renal perfusion pressure is reduced, secretion of prostaglandins (PGs) E_2 and I_2 from the stenotic kidney is increased [1–4] as the secretion of renin increases. The increased synthesis of PGs has been thought to be due to increased levels of angiotensin II (Ang II) caused by high renin activity [5]. PGE_2 and PGI_2 stimulate renin release [4, 6] and Ang II stimulates renal synthesis of the PGs [4, 7, 8] pharmacologically, so PGs and the renin-angiotensin system may interact in the kidney with renal arterial stenosis. In the stenotic kidney, PGs further stimulate renin release, according to studies done with cyclooxygenase inhibitors [6, 9], but whether Ang II increases PG synthesis is not yet known, because the Ang II antagonists available have had agonistic action in certain conditions.

In addition, the degree of pressure reduction (renal arterial stenosis) giving maximum renal secretion of PGs is different from the degree giving maximum secretion of renin [10]. This phenomenon calls for further study of the effect of Ang II on renal synthesis of PGE_2 in response to pressure reduction.

Here, we investigated whether Ang II is the cause of the increased renal synthesis of PGs that occurs when renal perfusion pressure decreases, using two different kinds of Ang II antagonists, losartan potassium (DuP 753; new nonpeptide) [11] and saralasin (peptide).

Methods

Preparation of animals

Adult mongrel dogs of either sex (body wt 12 to 16 kg) were fed a standard laboratory chow, which was withheld starting 18 hours before the experiments, and were given free access to water. The dogs were anesthetized with intravenous sodium pentobarbital (30 mg/kg). The trachea was cannulated and the dogs were ventilated mechanically with a Harvard respirator (Model 607). Polyethylene catheters were placed in the right brachial artery and vein for measurement of blood pressure and for infusion of saline (1 ml/min) or a drug, respectively. Systemic blood pressure was continuously monitored with a pressure transducer (P23ID, Viggo Spectramed) connected to a catheter, the tip of which was placed in the aorta. A catheter was inserted into the right femoral artery and the tip was placed in the abdominal aorta for aortic blood sampling. The left kidney was exposed through a left flank incision, and all visible nerve fibers around the renal artery were dissected to prevent the renal nerves from affecting the actions of the drugs used. An electromagnetic flow probe was placed around the renal artery, and the left renal blood flow was continuously recorded with an electromagnetic flowmeter (Nihon Kohden MFV-3200, Tokyo, Japan). A 23-gauge curved needle was inserted into the renal artery just distal to the flow probe for infusion of saline or drug solutions and for monitoring of the renal perfusion pressure. A constrictor device was placed around the renal artery proximal to the flow probe. Graded extraluminal constriction of the renal artery was produced by the tying of a silk suture tightly around the vessel, and the suture tension was regulated with a cylindrical plastic tube and a screw cock. This device produced varying degrees of stable stenosis of the renal artery. A polyethylene catheter was inserted into the left ureter so as not to interfere with the urine flow. The left renal vein was cannulated via the gonadal vein for collection of renal venous blood. More than one hour after surgery ended, experiments were started.

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Experimental protocol

Different dogs were used in each experiment.

Assessment of renal secretion of PGE_2 and renin and plasma levels of Ang II in response to decreased renal perfusion pressure. In six dogs, after control blood sampling from the aorta and renal vein (8 ml each), renal perfusion pressure was reduced by the constrictor device in steps from the control pressure to about 75 and then to about 45 mm Hg; these pressures are within and below the autoregulatory range of renal blood flow, respectively. Blood in the two sites was sampled after 8 minutes of equilibration at each step of pressure. The blood samples were immediately placed in ice-cooled tubes containing ethylenediaminetetraacetic acid 2 Na (1 mg/ml). The plasma was separated and assayed for PGE_2, Ang II, and plasma renin activity (PRA). The systemic blood pressure, renal perfusion pressure, and renal blood flow were serially monitored during the study. The secretion rate of PGE_2 was calculated as: Secretion rate (pg/g of kidney/min) = [venous concentration (pg/ml plasma) − arterial concentration (pg/ml plasma)] × renal plasma flow (ml/min) ÷ renal weight (g). The renin secretion rate was also calculated by this formula.

Study with a PG synthesis inhibitor. In another group of six dogs, after the control sampling of blood, aspirin DL-lysine (54 mg/kg, Venopirin, Green Cross Corp., Osaka, Japan), a synthesis inhibitor of PGs, was injected intravenously. Twenty minutes later, aortic and renal venous blood was sampled, and the experiment described above was done as in the first six dogs.

Ang II infusion study. Ang II (human type; Peptide Institute, Inc., Osaka, Japan) was infused with an infusion pump into the left renal artery of five dogs first at the dose of 30 ng/min and then at the dose of 300 ng/min. (Ang II is the same in humans and dogs [12]). In the control phase, saline was infused (0.3 ml/min) into the left renal artery and blood was drawn from the aorta and the left renal vein (8 ml each). The saline was replaced by Ang II solution at the dose of 30 ng/min, and blood was sampled from the two sites 8 minutes after the replacement. Next, saline was used again for the intrarenal infusion for at least 30 minutes during the recovery phase. After blood sampling from the two sites of the recovery controls, Ang II was infused at the dose of 300 ng/min and blood sampling was done eight minutes after the start of the second infusion. The sampled blood was assayed for PGE_2, Ang II, and PRA.

Study with Ang II antagonists. Two kinds of Ang II antagonists (peptide and nonpeptide) were used. One was saralasin ([Sar^1, Ala^8]Ang II, Peptide Institute) and the other was losartan potassium (DuP 753: 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[(2′-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole, potassium salt; the gift of Dr. Timmermans, E.I. du Pont de Nemours & Co.). After control blood sampling, saralasin (3 μg/min, $N = 6$) or losartan (1 mg/min, $N = 5$) was infused into the left renal artery. Twenty minutes after the start of the infusion, aortic and left renal venous blood was sampled. Then the renal perfusion pressure was reduced in steps by the constrictor device, and blood in the two sites was collected as in the first study in this protocol. The inhibition by saralasin and losartan of Ang II was checked by monitoring of the renal blood flow before and after a single injection of Ang II (50 ng) into the left renal artery. We decided on the doses of these antagonists based on previous reports [13–16]. In anesthetized dogs, the intrarenal arterial infusion of saralasin at 3 μg/min completely blocks the effect of Ang II [13], and the intravenous infusion of saralasin at 3 to 10 μg/kg per minute blocks that effect in humans [14]. When given intravenously, losartan completely blocked the action of Ang II at 3 mg/kg [15]. For intrarenal arterial infusions, we gave 1 mg of losartan per minute.

Measurements of humoral factors

PRA was measured by a radioimmunoassay as reported elsewhere [17]. The plasma levels of Ang II [18] and PGE_2 [9] were also measured by radioimmunoassays reported elsewhere. In brief, for the measurement of Ang II, 2 ml of plasma was put on a Sep-Pak cartridge (Waters Associates, Milford, Massachusetts, USA) and the Ang II was eluted with 3 ml of an 80:19.9:0.1 (vol/vol/vol) mixture of methanol, water, and trifluoroacetic acid. After the extraction, the Ang II was purified by high-pressure liquid chromatography and radioimmunoassayed. For the measurement of PGE_2, 2 ml of plasma was put on a Bond-Elut C-18 cartridge column (200 mg, Analytichem Intl. Inc., Harbor City, California, USA) and the PGE_2 was eluted with ethyl acetate. Next, a Bond-Elut silica column (500 mg, Analytichem) was used for further purification of PGE_2. After the purification, the samples were assayed with a [^{125}I]PGE_2 radioimmunoassay kit (New England Nuclear Corp., Boston, Massachusetts, USA).

Statistical analysis

Results are expressed as means ± SEM. The values for PGE_2, PRA, Ang II, renal blood flow, and blood pressure before and after treatment (administration of aspirin or an Ang II antagonist and pressure reduction) were compared by randomized block analysis of variance followed by Student-Newman-Keuls's test for simultaneous multiple comparison. Ang II levels in aortic and renal venous plasma were compared by Student's paired *t*-test. Secretion rates of renin in the groups with and without aspirin treatment were compared by Student's *t*-test.

Results

Renal secretion of PGE_2 and renin, and Ang II levels in plasma

In anesthetized dogs, the basal secretion rate of PGE_2 was 14.7 ± 3.6 pg/g kidney per minute, and the PGE_2 secretion was increased about seven- and fourfold when renal perfusion pressure was reduced to 75 and 45 mm Hg, respectively (Fig. 1A). The amount of PGE_2 secretion at the perfusion pressure of 75 mm Hg was significantly larger than that at the pressure of 45 mm Hg. Aspirin DL-lysine completely inhibited the secretion of PGE_2 in response to pressure reduction (Fig. 1A). Basal renin secretion was 1.4 ± 0.7 ng/g kidney per minute, and the secretion increased depending on the degree of the reduction of renal perfusion pressure (Fig. 1B). The increase in the renin release was significantly inhibited by aspirin (Fig. 1B). Basal levels of Ang II in aortic and left renal venous plasma were 12.8 ± 3.2 and 6.6 ± 1.8 pg/ml, respectively. The Ang II level in the renal venous plasma was significantly lower ($P < 0.05$) than the level in the aortic plasma. When the perfusion pressure was

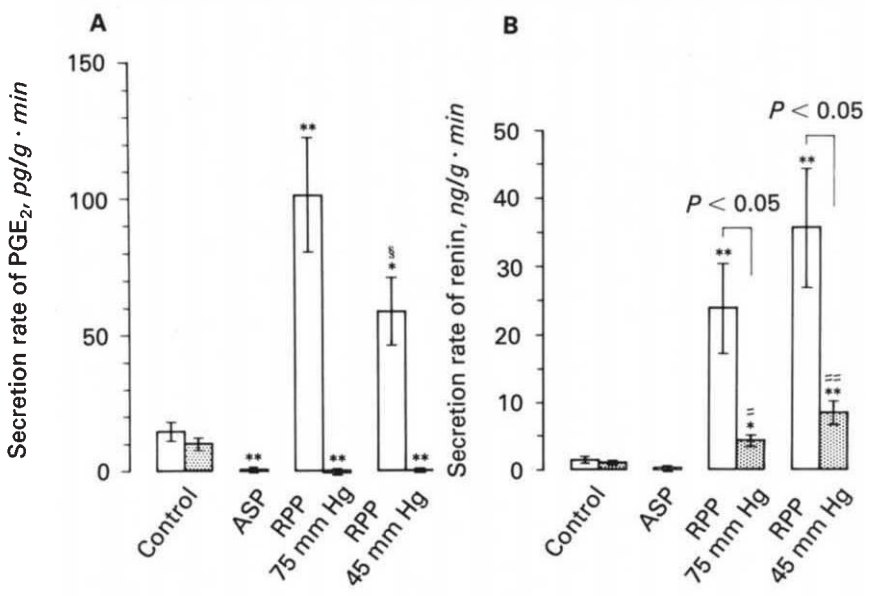

Fig. 1. *Renal secretion of prostaglandin E_2 (PGE_2; A) and renin (B) in response to pressure reduction.* The open columns show values without any drugs. The dotted columns (to the right in each pair of columns) show values with an intravenous injection of aspirin DL-lysine (ASP, 54 mg/kg) except for "Control", sampled before the injection. RPP, renal perfusion pressure. $*P < 0.05$ and $**P < 0.01$ compared with the controls. §$P < 0.05$ compared with the values in response to a renal perfusion pressure of 75 mm Hg. $\#P < 0.05$ and $\#\#P < 0.01$ compared with the values 20 min after treatment with ASP.

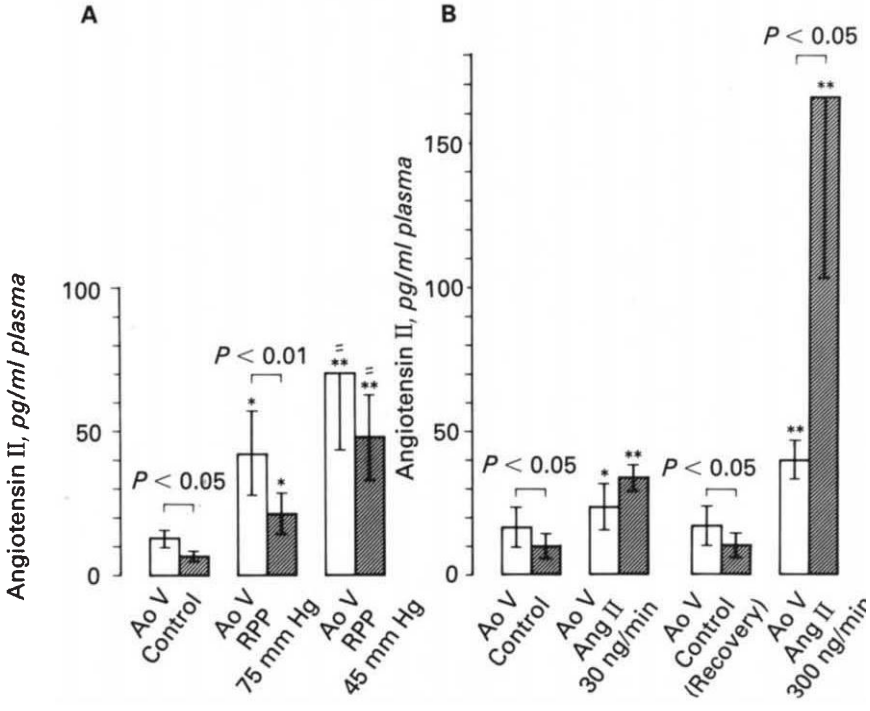

Fig. 2. *Angiotensin II (Ang II) levels in aortic plasma (□) and renal venous plasma (▨).* **A.** Ang II levels in response to decreased renal perfusion pressure. **B.** Changes in plasma levels of Ang II when authentic Ang II was injected into the renal artery at the dose of 30 and then 300 ng/min. Abbreviations are: Ao, aortic plasma; V, renal venous plasma; RPP, renal perfusion pressure. $*P < 0.05$ and $**P < 0.01$ compared with the controls or recovery. $\#P < 0.05$ compared with the values in response to renal perfusion pressure of 75 mm Hg.

reduced in steps, the Ang II levels at the two sites were significantly elevated in the same way (Fig. 2A).

Ang II infusion study

Figure 2B shows changes in the Ang II levels in aortic and renal venous plasma after the intrarenal arterial infusion of Ang II. The basal Ang II levels were 16.5 ± 7.3 and 9.8 ± 4.5 pg/ml in the aortic and the renal venous plasma, respectively. The venous plasma levels were lower ($P < 0.05$) than the aortic plasma levels. When Ang II was infused at the dose of 30 ng/min, Ang II levels at the two sites increased significantly; the level in the renal venous plasma was 33.7 ± 4.2 pg/ml. This value was close to the values after an increase in response to pressure reduction (Fig. 2A). However, the renal secretion of PGE_2 was not stimulated by the Ang II at 30 ng/min; the change was from 9.1 ± 3.0 to 13.3 ± 5.6 pg/g kidney per minute (Fig. 3). The higher dose of Ang II (300 ng/min) increased the Ang II level in the renal venous plasma to 166 ± 63 pg/ml. This large amount of Ang II somewhat increased the renal secretion of PGE_2, from 11.5 ± 3.2 to 37.9 ± 14.9 pg/g kidney per minute (P

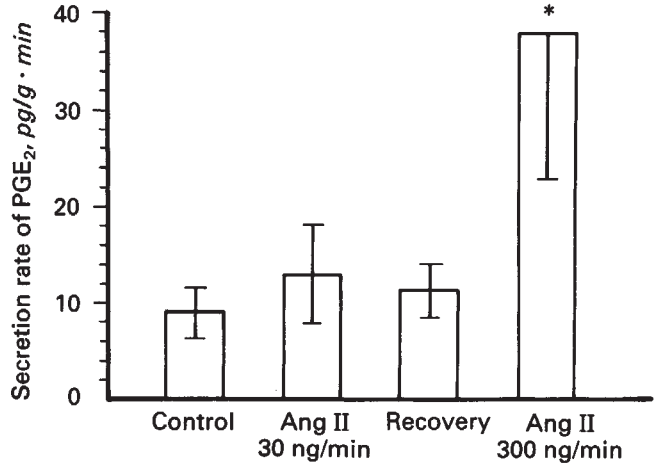

Fig. 3. *Renal secretion of prostaglandin E_2 (PGE_2) before and during intrarenal arterial infusion of angiotensin II* (Ang II). $^*P < 0.05$ compared with recovery.

< 0.05; Fig. 3). Changes in renal blood flow caused by the infusion of Ang II were from 3.4 ± 0.3 to 2.8 ± 0.3 ml/g kidney per minute ($P < 0.05$) at the dose of 30 ng/min and then from 3.5 ± 0.3 to 2.3 ± 0.2 ml/g kidney per minute ($P < 0.01$) at the dose of 300 ng/min. The blood flow was measured before and 8 min after the start of infusion at each dose, as described in **Methods**.

Study with Ang II antagonists

It was confirmed beforehand that either saralasin or losartan completely blocked the action of a single injection of Ang II in decreasing the renal blood flow. The effects of saralasin and losartan on the renal secretion of PGE_2 in response to pressure reduction are shown in Figure 4. The intrarenal arterial infusion of either Ang II antagonist did not inhibit the PGE_2 secretion caused by the reduction in renal perfusion pressure. The secretion rate of PGE_2 was higher ($P < 0.01$) when the perfusion pressure was 75 mm Hg than when it was 45 mm Hg, as in the experiment without Ang II antagonists. The increase in renin secretion in response to pressure reduction was not affected by saralasin or losartan, either (Fig. 5).

Hemodynamic changes

Table 1 shows hemodynamic changes in response to decreased renal perfusion pressure with or without the drugs. When the renal perfusion pressure was reduced to about 75 mm Hg, renal blood flow was not changed significantly, but in dogs given aspirin beforehand, the flow decreased slightly ($P < 0.05$); in contrast, the renal blood flow increased ($P < 0.01$ and 0.05) in dogs given either saralasin or losartan. When the perfusion pressure was reduced to 45 mm Hg, the renal blood flow decreased to nearly half in all test groups. Systemic blood pressure in the group given no drug and the group given aspirin increased when renal perfusion pressure was decreased to 45 mm Hg. When an Ang II antagonist was given before and during the decrease in the renal perfusion pressure, this increase was blocked.

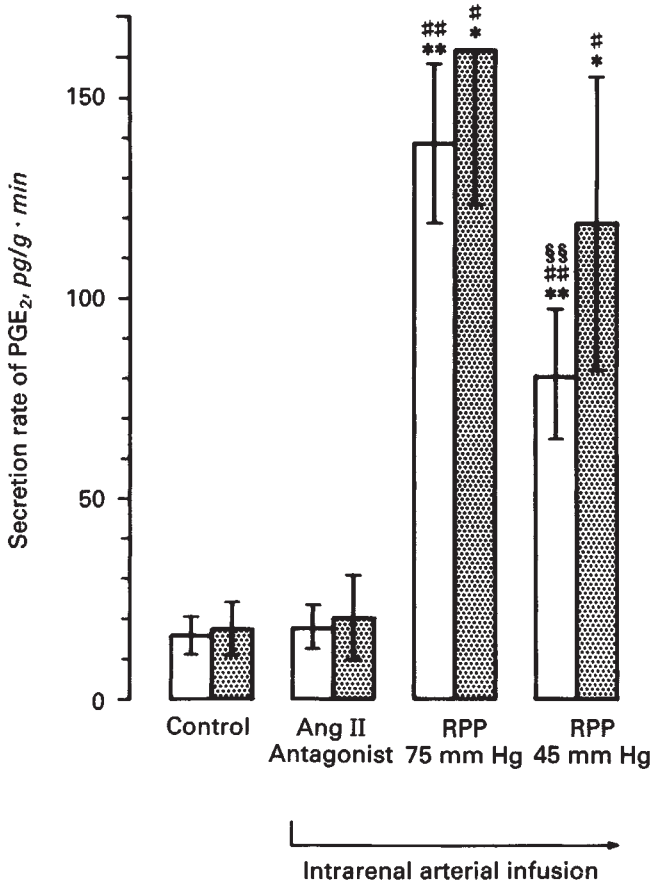

Fig. 4. *Renal secretion of prostaglandin E_2 (PGE_2) in response to decreased renal perfusion pressure (RPP) during treatment with an angiotensin II (Ang II) antagonist, saralasin (□, 3 μg/min) or losartan (▨, DuP 753, 1 mg/min).* $^*P < 0.05$ and $^{**}P < 0.01$ compared with the controls. $\#P < 0.05$ and $\#\#P < 0.01$ compared with the values after the start of injection of the Ang II antagonist. §§$P < 0.01$ compared with values in response to RPP of 75 mm Hg.

Discussion

We found no evidence for a contribution by Ang II to increased renal synthesis of PGE_2 in response to pressure reduction.

Pharmacologically, Ang II stimulates the renal synthesis of PGE_2 both in vivo [4, 7, 8, 19] and in vitro [20]. Thus, it has been believed that the renal secretion of PGE_2 in response to decreased perfusion pressure is due to increased Ang II, occurring via the increased release of renin [5]. Pathophysiologically, however, this might not actually occur, because there is a dissociation between the peaks of renal secretion of PGE_2 and renin in response to the reduction of renal perfusion pressure. In anesthetized dogs, renal secretion of PGs is maximum when the renal perfusion pressure is 60 to 77 mm Hg, which is the borderline pressure needed to maintain the renal blood flow, but the ipsilateral release of renin increases in proportion to the pressure reduction [10]. This phenomenon was seen again in this study. There are both PG-dependent and PG-independent (baroreceptor) mechanisms of renin release in response to decreased renal perfusion pressure [6, 20]. So, the

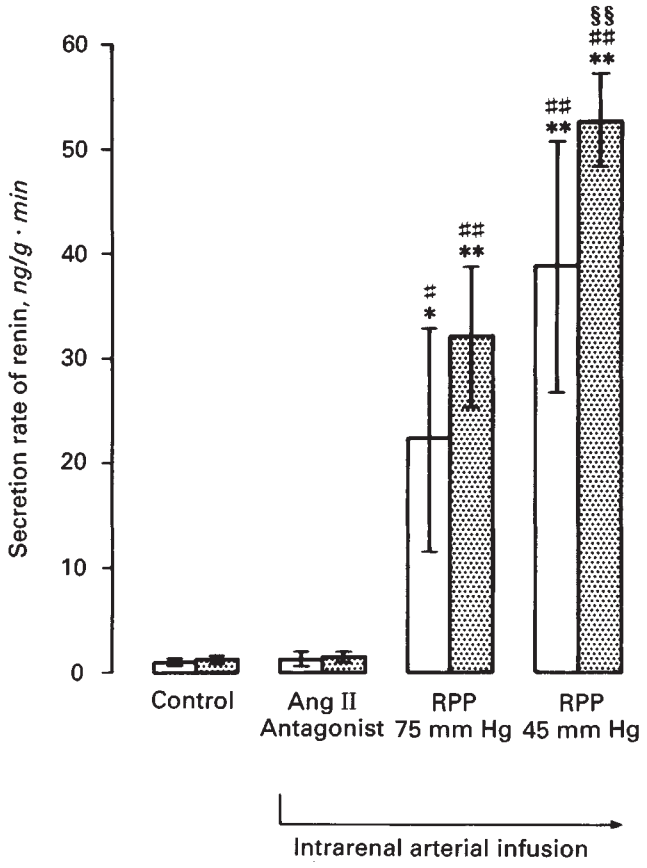

Fig. 5. *Renal secretion of renin in response to decreased renal perfusion pressure (RPP) during treatment with an angiotensin II (Ang II) antagonist, saralasin (□, 3 μg/min) or losartan (▨, DuP 753, 1 mg/min).* $*P < 0.05$ and $**P < 0.01$ compared with the controls. $\#P < 0.05$ and $\#\#P < 0.01$ compared with the values after the start of an injection of the Ang II antagonist. $\S\S P < 0.01$ compared with the values in response to RPP of 75 mm Hg.

Table 1. Hemodynamic changes caused by renal arterial constriction with and without treatment with aspirin or an angiotensin II antagonist

	Control	Treatment with a drug	First pressure reduction	Second pressure reduction
Renal perfusion pressure (mean) *mm Hg*				
No drug	124 ± 4		74 ± 1[b]	45 ± 2[b]
Aspirin	120 ± 3	126 ± 3	78 ± 3[b,d]	48 ± 2[b,d]
Saralasin	122 ± 6	122 ± 5	73 ± 1[b,d]	43 ± 1[b,d]
Losartan	126 ± 6	126 ± 5	74 ± 2[b,d]	47 ± 1[b,d]
Renal blood flow *ml/g/min*				
No drug	3.2 ± 0.3		3.5 ± 0.3	1.8 ± 0.2[b]
Aspirin	3.3 ± 0.4	2.9 ± 0.5	2.6 ± 0.5[a]	1.4 ± 0.2[b,d]
Saralasin	3.0 ± 0.3	3.1 ± 0.4	4.1 ± 0.5[b,d]	2.4 ± 0.3[b,d]
Losartan	3.7 ± 0.3	4.0 ± 0.4	4.7 ± 0.5[a,c]	2.7 ± 0.3[b,d]
Systemic blood pressure (mean) *mm Hg*				
No drug	124 ± 4		126 ± 4	140 ± 5[b]
Aspirin	120 ± 3	126 ± 2[b]	128 ± 3[b]	132 ± 3[b,d]
Saralasin	122 ± 6	122 ± 5	121 ± 5	121 ± 5
Losartan	126 ± 6	126 ± 5	126 ± 5	127 ± 5

Values are means ± SEM. These data were compared by randomized block analysis of variance followed by Student-Newman-Keuls's test for simultaneous multiple comparison.

[a] $P < 0.05$ and [b] $P < 0.01$ relative to control values

[c] $P < 0.05$ and [d] $P < 0.01$ relative to values for treatment with the drug before pressure reduction

phenomenon does not suggest that PGE_2 is not involved in the accelerated release of renin. The results reported here for the study with aspirin also confirmed the existence of those two mechanisms of PG-dependent and PG-independent renin release (Fig. 1B). They are not consistent with Ang II stimulating PGE_2 synthesis if the Ang II level in the kidney increases (as renin release does) in proportion to the pressure reduction.

Our study showed that the increase in Ang II in the renal venous plasma was parallel to the increase in renin secretion. However, the Ang II concentrations in renal venous plasma were lower than those in the aortic plasma (Fig. 2A). This is consistent with the previous findings in anesthetized dogs [21] and also in humans [22]. This phenomenon may reflect the metabolism of Ang II in the kidney being greater than its production; more than 90% of circulating Ang II is metabolized in the kidney, but Ang II formed within the kidney is a consequence of increased intrarenal Ang I generation due to increased renin release [21]. Thus, the changes in the Ang II level in renal venous plasma might reflect the renal synthesis and metabolism of Ang II, and we therefore used intrarenal Ang II infusion to investigate the amount of Ang II needed to stimulate PGE_2 synthesis by measurement of Ang II in the renal venous plasma. The continuous infusion of Ang II (30 ng/min) into the kidney decreased the renal blood flow by only 18%, and increased the renal venous Ang II to a level higher than the level reached in response to the reduction of renal perfusion pressure to 75 mm Hg. The amount of Ang II infused did not increase the renal secretion of PGE_2. In previous studies [7, 8, 19] and in this study as well, pharmacological, not physiological, amounts of Ang II were needed for the stimulation of renal PGE_2 synthesis.

In anesthetized and laparatomized dogs, basal renal PGE_2 production is stimulated without renal arterial constriction, and the amount of Ang II that would need to be infused to increase renal PGE_2 would be larger than in conscious dogs not undergoing surgery. But when renal perfusion pressure was 75 mm Hg, renal PGE_2 production was much larger than that caused by Ang II infusion. In addition, renal venous plasma levels of Ang II at that renal perfusion pressure were much less than those caused by exogenous Ang II infused at 300 ng/min. However, the concentration of Ang II in the renal venous plasma may not necessarily be proportional to the effective concentrations at the sites of production and action. A further possibility is that tissue rather than circulating Ang II is responsible for physiological actions such as the stimulation of PG synthesis [23–25]. Thus, results from the above experiment could not rule out the possibility of a pathophysiological role of Ang II in PG stimulation in response to pressure reduction.

Neither kind of Ang II antagonist that we used suppressed the renal synthesis of PGE_2 in response to pressure reduction. The doses of saralasin and losartan were high enough to inhibit the action of Ang II, according to results of reported studies [13–16], and both drugs acted as antagonists when Ang II was

given as a bolus injection. Further, both losartan and saralasin prevented the elevation of blood pressure caused by renal arterial constriction (Table 1). Recently, it has been reported that there are two subtypes of Ang II receptors, AT_1 and AT_2 [26, 27]. The receptors that mediate Ang-II-induced vasoconstriction and PGE_2 synthesis are all of the AT_1 type [28]. Losartan is a selective AT_1 receptor antagonist, and saralasin is a nonselective one. The antagonizing action of these drugs on the stimulation of PGE_2 synthesis by Ang II has already been demonstrated [28]. We also found that losartan and saralasin blocked the effect of an intrarenal arterial Ang II infused in a large dose on the stimulation of renal PGE_2 production (data not shown). In our study, the renal site of PGE_2 synthesis in response to pressure reduction was not identified, but the antagonists to Ang II seemed to reach the site that was stimulated by Ang II, as aspirin did. Therefore, when levels of Ang II are increased in response to pressure reduction, if renal PGE_2 production increases because of the pathophysiological increase in Ang II, these Ang II antagonists must suppress the release of PGE_2 from the stenotic kidney. These findings suggest that Ang II does not stimulate the renal synthesis of PGE_2 that occurs in response to pressure reduction, or else that it does not have a major role in such synthesis of PGE_2. The studies with the two kinds of Ang II antagonists used here provided more direct evidence of the effects of Ang II on PG synthesis than studies that might be done with renin inhibitors or angiotensin converting enzyme inhibitors (the latter influence bradykinins).

Losartan and saralasin did not affect renin release in response to pressure reduction, which was consistent with a previous report [13]. When renal perfusion pressure was reduced to about 75 mm Hg (the borderline of the autoregulation of renal blood flow), aspirin decreased the renal blood flow, but the Ang II antagonists increased it. These results support that the increase in renal PG is independent of any increase in Ang II in response to pressure reduction.

Ang II does, of course, have a physiological effect in stimulating PG synthesis. However, our study suggests that when renal perfusion pressure is reduced, increased renal PGE_2 further stimulates renin release, but that the greater part of PGE_2 seems to be independent of Ang II.

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